REMARKS

Claims 1, 3, 4, 12, 18, 22, 23, and 26-48 were pending in the application upon issuance of the Office Action. Claims 1, 3, 12, 18, 22 and 26-38 have been amended, and new claims 49-56 have been added. Following entry of the foregoing amendments, claims 1, 3, 4, 12, 18, 22, 23, and 26-56 will remain pending in the application.

Support for the new and amended claims may be found throughout the specification and claims as originally filed, including, for example, at page 32, lines 22-26; page 33, lines 15-17; page 36, lines 29-31; and page 49, lines 12-13. No new matter has been added to the application by way of these amendments.

The foregoing amendments have been made solely for the purpose of expediting prosecution of the present application and should in no way be construed as acquiescence to any of the Examiner's rejections in this or in any former Office Action issued in the present application. Applicants reserve the right to pursue the subject matter of the claims as originally filed in this application or in another related application.

In view of the foregoing claim amendments and the remarks set forth below, Applicants respectfully submit that the claims are in condition for allowance.

Withdrawal of Certain Rejections

Applicants gratefully acknowledge the withdrawal of the rejection of claims 4, 15, 18, 20 and 22-23 under 35 U.S.C. § 112, second paragraph; the rejection of claims 5 and 15 under 35 U.S.C. § 112, second paragraph; the rejection of claims 4, 15, 18, 20 and 22-23 under 35 U.S.C. § 112, first paragraph; the rejection of claims 2 and 6 under 35 U.S.C. § 112, first paragraph; the rejection of claims 1-4, 6, 12, 14-15, 18, 20 and 22-23 under 35 U.S.C. § 103(a) as being unpatentable over Ogilvie *et al.*, Br. J. Dermatol., 144(3):587-89 (2001) in view of Salfeld *et al.* [a] (WO 97/29131) or [b] (US 6,509,015) and Smith *et al.*, Arthritis Rheum. 23(8):961-962 (1980); the rejection of claims 1-4, 6, 12, 14-15, 18, 20 and 22-23 on the ground of nonstatutory obviousness-type double patenting as being un patentable over claims 1-7, 36-39 and 69 of U.S. Patent No. 6,509,015 in view of Ogilvie *et al.* and Smith *et al.*; the provisional rejection of claims 1-4, 6, 12, 14-15, 18, 20 and 22-23 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 2, 11-15, 22-23, 73-77, 80, 82-83, 89-94, 96 and 99 of USSN 10/163,657 in view of Ogilvie *et al.*, Salfeld *et al.*, and Smith *et al.*; the

provisional rejection of claims 1-4, 6, 12, 14-15, 18, 20, and 22-23 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 4-8 and 10-14 of USSN 11/435,844 in view of Ogilvie *et al.* and Smith *et al.*; the provisional rejection of claims 1-4, 6, 12, 14-15, 18, 20 and 22-23 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 15, 19, 56, 66, 77 and 87 of USSN 11/233,252 in view of Ogilvie *et al.*, Salfeld *et al.* [a], and Smith *et al.*; the provisional rejection of claims 1-4, 6, 12, 14-15, 18, 20, and 22-23 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-2 and 4-14 of USSN 10/622,932 in view of Ogilvie *et al.* and Smith *et al.*; the provisional rejection of claims 1-4, 6, 12, 14-15, 18, 20, and 22-23 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-11 of USSN 10/623,075 in view of Ogilvie *et al.* and Smith *et al.*; and the provisional rejection of claims 1-4, 6, 12, 14-15, 18, 20, and 22-23 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 3-14 and 16 of USSN 10/623,318 in view of Ogilvie *et al.* and Smith *et al.*.

Objections to the Specification

Applicants acknowledge the Examiner's objection to the specification as disclosing various non-provisional U.S. Patent Application numbers whose status requires updating, which was maintained by the Examiner for convenience. To Applicants' knowledge the status of all U.S. Patent Applications listed in the instant specification is up to date. Applicants will continue to update the specification to indicate changes in the status of any U.S. Patent Applications referenced therein as necessary.

The Examiner has additionally objected to the title of the application as allegedly not being descriptive. Applicants have amended the title to "Treatment of Psoriatic Arthritis using Human TNFα Antibodies" in accordance with the Examiner's recommendation, thereby obviating the objection.

Rejection of Claims 1, 3, 4, 12, 18, 22, 23, and 26-48 Under 35 USC § 103(a)

The Examiner has rejected claims 1, 3, 4, 12, 18, 22, 23, and 26-48 under 35 USC 103(a) as allegedly being unpatentable over (1) Ogilvie *et al.* (British Journal of Dermatology, 144(3):587-589, March 2001) in view of Salfeld *et al.* ([a] WO 97/29131 or [b] U.S. 6,509,015), Smith *et al.* (Arthritis Rheum. 23(8):961-962, August 1980) and Keystone *et al.* (The Fully

Human Anti-TNF Monoclonal Antibody, Adalimumab (D2E7), Dose Ranging Study: The 24-Week Clinical Results in Patients with Active RA on Methotrexate Therapy (The ARMADA Trial), *Presented at the Annual Meeting of the European League Against Rheumatoid Arthritis (EULAR), Prage, Czech Republic, 2001*). In particular, the Examiner indicates that it would have been *prima facie* obvious to one skilled in the art at the time the invention was made to produce a method of treating psoriatic arthritis in a human patient comprising biweekly, subcutaneous administration of the D2E7 anti-TNFα antibody or fragments thereof at a dosage of 20 mg, 40 mg or 80 mg, in view of the combined teachings of these references.

Applicants respectfully traverse this rejection. As set forth in MPEP §2143, "[t]o establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine the reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations."

Amended claims 1, 3, 4, 12, 22, 23, 26-18 each require biweekly, subcutaneous administration of a dose of a human anti-TNFα antibody, or antigen binding fragment thereof, to a subject having PsA, *wherein the dosage of the human anti-TNFα antibody, or antigen-binding fragment thereof, comprises 10-150 mg and is the same dosage throughout the course of biweekly treatment*. Amended claim 18 requires biweekly, subcutaneous administration of a dose of about 40 mg of adalimumab for treating a subject suffering from PsA. Moreover, new claims 49-53 describe a method of treating PsA *consisting of biweekly, subcutaneous administration of a dosage consisting of 10-150 mg* of a human anti-TNFα antibody, or antigen binding fragment thereof. New claims 54-56 further describe a method of treating PsA in a subject comprising subcutaneous administration of a dose of a human anti-TNFα antibody, or antigen binding fragment thereof, to a subject, wherein the *dosage of the human anti-TNFα antibody, or antigen-binding fragment thereof, comprises 10-150 mg and is the same dosage throughout the course of treatment*.

Applicants respectfully submit that the references alone or in combination fail to establish a *prima facie* case of obviousness over the amended claims. Ogilvie *et al.*, the primary reference which forms the basis of the rejection, describes improvements in PASI scores in six patients having psoriatic arthritis following administration of the *chimeric monoclonal anti-*

TNFα antibody infliximab at a weight-based dosage of 5 mg/kg at weeks 0, 2 and 6. Ogilvie *et al.* does not teach or suggest a method of treating psoriatic arthritis (or inhibiting human TNFα activity in a subject suffering from PsA) by subcutaneous administration of a dosage of human anti-TNFα antibody, or antigen-binding portion thereof, wherein the dosage of the human anti-TNFα antibody, or antigen-binding portion thereof, comprises 10-150 mg and is the same dosage throughout the course of treatment, as required by the amended claims. In contrast, the Ogilvie reference describes a weight-based dosing scheme which is not equivalent to Applicants' claimed invention. Moreover, Ogilvie fails to teach or suggest a biweekly dosing regimen as required by claims 1, 3, 4, 12, 18, 22, 23, 26-48 and new claim 49-53, and fails to teach a human anti-TNFα antibody, or antigen-binding portion thereof.

To make of up for the deficiencies of Ogilvie, the Examiner relies upon Salfeld for teaching a human anti-TNFα antibody, or antigen-binding portion thereof, and Keystone for teaching a biweekly dosing regimen.

The substitution of the human TNFα antibody (D2E7) taught by Salfeld *et al.* for use in treating psoriatic arthritis as taught by Ogilvie *et al.* for the purported benefit of avoiding any unwanted immune reaction still fails to render the presently claimed invention *prima facie* obvious. Salfeld *et al.* describes fully human neutralizing anti-TNFα antibodies with high affinity for TNFα. Salfeld does not teach a dosage of a human anti-TNFα antibody, or antigen-binding portion thereof, comprising a dosage of 10-150 mg that is independent of body weight, in accordance with the claims. This deficiency is not remedied by the teachings of Smith *et al.*, who reports improvement in five cases of psoriatic arthritis during ibuprofen therapy.

Given the observation that six patients experienced a clinical improvement in their PsA after three intravenous infusions of 5 mg/kg infliximab at weeks 0, 2 and 6 (Ogilvie *et al.*), combined with generalized teachings regarding human TNFα antibodies (Salfeld *et al.*), one of ordinary skill in the art would not have concluded that administration of a human anti-TNFα antibody at a dosage comprising 10-150 mg independent of body weight would be efficacious in treating psoriatic arthritis, either alone or in combination with ibuprofen (Smith *et al.*).

Keystone *et al.* fails to make up for the deficiencies of the combined teachings of Ogilvie *et al.*, Salfeld *et al.*, and Smith *et al.* Applicants note that this reference is not directed to the treatment of psoriatic arthritis. Rather, Keystone *et al.* describe the results of a clinical trial for *rheumatoid arthritis,* a disease that is distinct from *psoriatic arthritis*. While Keystone *et al.*

reports that subcutaneous, biweekly administration of D2E7 in combination with methotrexate was more efficacious than placebo in treating patients with *rheumatoid arthritis*, there is nothing in the combined teachings of the references that suggests that this regimen could successfully be used to treat *psoriatic arthritis*. Indeed, dosage regimens can vary significantly by disease, in terms of both dosage amount and frequency. Applicants respectfully submit that the references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention.

Moreover, Applicants submit that agents known in the art to treat more than one disorder do not necessarily have the same dosing regimen. For example, the recommended dosage regimen for the chimeric TNFα antibody, infliximab, for the treatment of rheumatoid arthritis is 3 mg/kg at 0, 2 and 6 weeks followed by 3 mg/kg every 8 weeks, whereas the recommended dosage regimen of the same drug for psoriatic arthritis is 5 mg/kg at 0, 2 and 6 weeks followed by 5mg/kg every 8 weeks, *an increase of 66% with respect to the quantity of the same drug administered for the treatment of RA* (see, for example, http://www.rxlist.com/remicade-drug.htm, page 2, attached herewith as Appendix A). Applicants further note that the dosage regimen of infliximab for treatment of ankylosing spondylitis is 5mg/kg at 0, 2 and 6 weeks followed by 5 mg/kg every 6 weeks (see, for example, Appendix A, page 2), further supporting Applicants' assertion that the dosing particulars of agents known in the art to treat rheumatoid arthritis can not simply be extrapolated to the treatment of other diseases or conditions. Accordingly, Applicants respectfully submit that one of average skill could not have reasonably predicted that the dosage regimen of the human anti-TNFα antibody D2E7 described by Keystone *et al.* as being effective for treating *rheumatoid arthritis* when administered in combination with methotrexate would be successful in treating *psoriatic arthritis* based on Ogilvie's observation that symptoms of psoriatic arthritis improved following administration of infliximab at a weight-based dosage of 5 mg/kg at weeks 0, 2 and 6.

In view of the foregoing, Applicants respectfully request that the rejection of claims 1, 3, 4, 12, 18, 22, 23, and 26-48 under 35 U.S.C. § 103(a) be reconsidered and withdrawn.

Rejection of Claims 1, 3, 4, 12, 18, 22, 23, and 26-48 on Ground of Non-Statutory Obviousness-Type Double Patenting

The Examiner has rejected claims 1, 3-4, 12, 18, 22-23 and 26-48 on the ground of nonstatutory obviousness-type double patenting as allegedly being unpatentable over claims 1-7,

36-39 and 69 of U.S. Patent No. 6,509,015 (Salfeld *et al.* [b], described above) in view of Ogilvie *et al.*, Smith *et al.,* and Keystone *et al.* (described above). In particular, the Examiner asserts that the indicated claims of Salfeld *et al.* are drawn to methods involving administration of a human anti-TNFα antibody. While the Examiner acknowledges that Salfeld *et al.* does not teach a method of treating psoriatic arthritis in a patient comprising biweekly, subcutaneous administration of a specified dosage of an anti-TNFα antibody, the Examiner asserts that these deficiencies are made up for in the teachings of Ogilvie *et al.* and Keystone *et al.* Applicants traverse this rejection.

As noted above, Keystone *et al.* describes the results of a clinical trial for *rheumatoid arthritis* in which the anti-TNFα antibody D2E7. Keystone *et al.* does not teach or suggest the use of a human anti-TNFα antibody administered subcutaneously at a dosage of 10-150 mg where the dosage is the same throughout the course of treatment for *psoriatic arthritis*, as required by the claims. The Examiner relies upon Ogilvie *et al.* for teaching a method of treating psoriatic arthritis. Ogilvie *et al.* likewise fails to teach or suggest a method of treating psoriatic arthritis using a human anti-TNFα antibody administered as a dosage of 10-150 mg independent of body weight, as noted above. Furthermore, dosage regimens can vary significantly by disease, in terms of both dosage amount and frequency, and, therefore, a person of skill in the art would not simply extrapolate a dosing regimen from one disease to a different disease with a reasonable expectation of success. This assertion is evidenced by Appendix A, enclosed herewith, which indicates that the quantity of the chimeric anti-TNFα antibody infliximab is increased by 66% for the treatment of psoriatic arthritis as compared with rheumatoid arthritis. Accordingly, absent the teachings of the specification, a person of skill in the art, given the teachings of Salfeld *et al.*, Keystone *et al.* and Ogilvie *et al.*, would have no expectation of success in treating psoriatic arthritis by administering human TNFα antibody at a dosage of 10-150 mg independent of body weight on a biweekly, subcutaneous dosing regimen, as required by the claims. Accordingly, Applicants request that the rejection of the pending claims on the ground of nonstatutory obviousness-type double patenting be reconsidered and withdrawn.

Provisional Rejection of Claims 1-4, 6, 12, 14-15, 18, 20, and 22-23 on the Ground of Nonstatutory Obviousness-Type Double Patenting

The rejection of claims 1-4, 6, 12, 14-15, 18, 20 and 22-23 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 3-10, 16-21, 78-79, 81, 84, 86-88, 95, 97-98 and 100-104 of copending Application No. 10/163,657 in view of Ogilvie *et al.*, Salfeld *et al.* [a] and Smith *et al.* was maintained. In addition, the Examiner has provisionally rejected claims 1, 3, 4, 12, 18, 22, 23 and 26-48 as being unpatentable on the ground of nonstatutory obviousness-type double patenting over claims 1, 4, 5, 8-11, 14, 38, 39, 49, 50, 52, 53 and 55-57 of copending Application No. 11/435,844 in view of Ogilvie *et al.*, Smith *et al.*, and Keystone *et al.* The Examiner has also provisionally rejected claims 1, 3, 4, 12, 18, 22, 23 and 26-48 as being unpatentable on the ground of nonstatutory obviousness-type double patenting over claims 15, 19, 56, 66, 77, and 87 of copending Application No. 11/233,252 in view of Ogilvie *et al.*, Salfeld *et al* (a), and Smith *et al.*

Applicants note that the foregoing rejections are provisional in nature and respectfully submit that they will be further addressed when appropriate, *i.e.*, when the nonstatutory obviousness-type double patenting rejection is the only rejection remaining in the later-filed application (MPEP § 804 I.B.).

If a telephone conversation with Applicant's attorney would help expedite the prosecution of the above-identified application, the Examiner is urged to call Applicant's attorney at (617) 227-7400.

Dated: December 9, 2008

Respectfully submitted,
Electronic signature:
/ Cristin Howley Cowles, Ph.D. /
Cristin Howley Cowles, Ph.D.
Registration No.: 55,281
LAHIVE & COCKFIELD, LLP
One Post Office Square
Boston, Massachusetts 02109-2127
(617) 227-7400
(617) 742-4214 (Fax)
Attorney/Agent For Applicant